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Analysis of a bacteria–immunity model with delay quorum sensing ☆

Zhang Zhonghua [a,*], Peng Jigen [b], Zhang Juan [c]

[a] *Department of Applied Mathematics, Xi'an Jiaotong University, Xi'an 710049, China*
[b] *Research Center for Applied Mathematics, Xi'an Jiaotong University, Xi'an 710049, China*
[c] *Department of Mathematics, North China Electric Power University, Beijing 102206, China*

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Abstract

A bacteria–immunity model with bacterial quorum sensing is formulated, which describes the competition between bacteria and immune cells. A distributed delay is introduced to characterize the time in which bacteria receive signal molecules and then combat with immune cells. In this paper, we focus on a subsystem of the bacteria–immunity model, analyze the stability of the equilibrium points, discuss the existence and stability of periodic solutions bifurcated from the positive equilibrium point, and finally investigate the stability of the nonhyperbolic equilibrium point by the center manifold theorem.

Keywords: Quorum sensing; Distributed delay; Hopf bifurcation; Center manifold; Stability; Immunity

1. Introduction

All of living organisms are continuously exposed to the substances that are capable of causing them harm. Most organisms protect themselves against such substances in more than one way (e.g. with physical barriers or chemicals). Animals with backbones, called vertebrates, have these types of general protective mechanisms, but they also have a more advanced protective system called immune system. The immune system is a complex network of organs containing cells that recognize foreign substances in body and destroy them. It protects vertebrates against pathogens, or infectious agents, such as viruses, bacteria, fungi, and other parasites. There are two basic kinds of immunity [1,2]: the innate immunity and the adaptive one. The innate immunity is the first line of defence, it is nonspecific, i.e. it is against any pathogens that enter the body other than against specific invaders, and it can suffice to clear the pathogens in most cases, but sometimes it is insufficient. In fact, some pathogens may possess ways to overcome the innate immunity and successfully colonize and infect the host. When the innate immunity fails, a completely different cascade of events ensues leading to adaptive immunity. Unlike the innate immunity, the adaptive immunity is specific, i.e. it recognizes and destroy specific pathogen.

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* Corresponding author.
E-mail address: wwwzhonghua@sohu.com (Z. Zhang).

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Quorum sensing is a process that enables bacteria to communicate using secreted signaling molecules called autoinducers [3]. This process enables a population of bacteria to regulate gene expression collectively and, therefore, control behavior on a community-wide scale. The quorum sensing mechanism was first observed in the marine bacterium Vibrio fisheri around 30 years ago [4,5]. In the sequel, many other species have been discovered to exhibit quorum sensing behavior, including major human pathogens such as Staphylococcus aureus and Pseudomonas aeruginosa. In the last several years, quorum sensing mechanism has received much attraction [6–11], etc. Firstly, J.P. Braselton and P. Waltman [6] formulated a model with dynamically allocated inhibitor production and studied its qualitative properties. Then, to obtain a deeper understanding of how and when this mechanism works, J.D. Dockery and J.P. Keener [7] were devoted to developing and studying an ODE and a PDE mathematical models for quorum sensing in Pseudomonas aeruginosa. A.J. Koerber et al. [8] presented a mathematical model for the early stages of the infection process by Pseudomonas aeruginosa in burn wounds which accounts for the quorum sensing and the diffusion of signalling molecules in the burn-wound environment, and further the effects of important parameters on the dynamic properties of the model are discussed in detail. P. Fergola et al. [9] founded an allelopathic competition model in which a distributed delay term models a linear quorum sensing mechanism which regulates the delayed allelochemicals' production process and then proved the unique-existence of the positive solution and the stability of biologically meaningful steady-state solutions. K. Anguige et al. [10] constructed a multi-phase mathematical model of quorum sensing in a maturing Pseudomonas aeruginosa biofilm to investigate the effect of anti-quorum sensing and antibiotic treatments on exopolysaccharide concentration, signal level, bacterial numbers and biofilm growth rate. Recently, a model describing the competition between bacteria and immunity system was formed by Zhang et al. [11], and the stability of the meaningful steady-state solutions is discussed.

In this paper, considering the quorum sensing mechanism of bacteria in the competition between bacteria and immunity system and introducing a distributed delay to describe the time in which bacteria receive signal molecules and then combat with immune cells, we formulate a bacteria–immunity model with delay quorum sensing. Subsequently, we analyze the stability of the equilibria, and discuss the existence and stability of periodic solutions in the neighborhood of the positive equilibrium by using the inverse of the average delay as a bifurcation parameter.

It is well known that mathematical model is an important tool to understand the transmission characteristics of epidemic diseases, identify their trends, make general forecasts and estimate the uncertainty in forecasts [12]. In fact, deterministic epidemiology modeling seems to start in the 20th. In 1906 Hamer [13] built and analyzed a discrete time model to investigate the recurrence of measles, and which may be the first one to assume that the incidence (number of new cases per unit time) depends on the product of the densities of the susceptible and infective. This assumption is still widely used in recent models. Another important work is owed to [14], in 1911 Ross was interested in the control of malaria and developed differential equation models for malaria as a host-vector disease. His results show that if the number of mosquitoes is less than a threshold the disease can be controlled. Subsequently, in 1927 and 1932 Kermack and McKendrick [15,16] respectively founded a *SIR* model and a *SIS* model by the method of compartment and proposed the theory of threshold which forms the foundation of the epidemic dynamics. It is in the middle of 20th, epidemic dynamic began to develop exponentially [12], and a tremendous variety of models have been formulated, mathematically analyzed and applied to infectious diseases, see ([4–11,17–23] and references therein). In the same time, lots of new factors such as passive immunity, gradual loss of vaccine and disease-acquired immunity, stages of infection, vertical transmission, disease vectors, macro-parasitic loads, age structure, social and sexual mixing groups, spatial spread, vaccination, quarantine, chemotherapy, etc. were involved in different models. For examples, pulse vaccination was considered in [17,18], stage-structure and pulse for pest management strategy were included in [19], and the effects of immunity were investigated in [11,20]. As a result, more and more valuable information are provided, and which help us to design practical strategies for the control and extinction of epidemic diseases.

This paper is arranged as follows: Section 2 formulates the model, Section 3 analyzes the local stability and Hopf bifurcation, Section 4 is the global stability of the positive equilibrium, Section 5 makes the conclusions.

2. Model formulation

In this section, considering the delay quorum sensing phenomena of bacteria and basing on [11], we formulate a mathematical model to characterize interaction between immune cells and bacteria.

We first denote the concentration at time t of uninfected target cells, infected target cells, bacteria, innate cells and adaptive cells, as $X_U(t)$, $X_I(t)$, $B(t)$, $I_R(t)$ and $I_A(t)$, respectively. Suppose the dynamic relations among them are as the following: Uninfected target cells have a natural turnover S_U and half-life μ_{X_U}, and can be infected (mass-action term $\alpha_1 X_U B$); infected target cells can be cleared by adaptive immune cells (mass action term $\alpha_2 X_I I_A$) or half-life μ_{X_I}; both innate and adaptive immune cells have a source term and a half-life time, for innate immunity, the source term S_{I_R}, which includes a wide range of cells involved in the first wave of defense of the host (e.g. natural killer cells, polymorphonuclear cells, macrophages and dendritic cells), and for adaptive immunity, the source term S_{I_A} represents that the memory cells are present, derived from a previous infection (or vaccination), a zero source means the first infection with this pathogen (i.e. there are no memory cells); Both the numbers of innate immune cells and adaptive cells are increased by the signals that we have captured by means of bacteria load; the bacteria population has a net growth term, represented by a logistic function $\alpha_{20}B(1-\frac{B}{\sigma})$ and is also cleared by innate immunity (mass action term $\alpha_3 B I_R$). We consider a mechanism named quorum sensing for bacteria, by which the bacteria control their growth rate or the expression of their genes in response to their own or the density of other microorganisms (e.g. bacteria, immune cells) in the environment. Further, we introduce a distributed delay to describe the time in which bacteria receive signal molecule and then combat with immune cells. The model is governed by

$$\begin{cases} \dfrac{dB(t)}{dt} = \alpha_{20}\left(1 + \displaystyle\int_{-\infty}^{t} \beta e^{-\beta(t-u)}\frac{B(u)}{B_0}\,du - \frac{B(t)}{\sigma}\right)B(t) - \alpha_3 B(t) I_R(t), \\ \dfrac{dX_U(t)}{dt} = S_U - \alpha_1 X_U(t) B(t) - \mu_{X_U} X_U(t), \\ \dfrac{dX_I(t)}{dt} = \alpha_1 X_U(t) B(t) - \alpha_2 I_A(t) X_I(t) - \mu_{X_I} X_I(t), \\ \dfrac{dI_R(t)}{dt} = S_{I_R} + \beta_1 B(t) - \mu_{I_R} I_R(t), \\ \dfrac{dI_A(t)}{dt} = S_{I_A} + \beta_2 B(t) - \mu_{I_A} I_A(t), \end{cases} \tag{2.1}$$

where α_{20} is the effective reproductive rate of bacteria (the reproduction rate minus the death rate), σ the effective carrying capacity of the environment, $\alpha_{20}B(t)(1-\frac{B(t)}{\sigma})$ the logistic growth of bacteria, $\alpha_{20}B(t)\int_{-\infty}^{t}\beta e^{\beta(t-u)}\frac{B(u)}{B_0}\,du$ the concentration of the bacteria competing with immune cells at time t, and which receive the signal molecules u time units ago, and B_0 a positive constant. Suppose all of parameters in system (2.1) are positive.

According to MacDonald [24], $\beta e^{-\beta s} > 0$ is called the weak delay kernel and the average delay τ_{ava} is defined as

$$\tau_{\text{ava}} = \int_0^{\infty} \beta s e^{-\beta s}\,ds = \frac{1}{\beta}.$$

The initial values for system (2.1) are

$$\begin{aligned} &B(s) = \psi(s), \quad s \in (-\infty, 0] \quad \text{with } \psi(0) > 0,\ \psi(s) \geqslant 0,\ s \in (-\infty, 0),\ \psi(\cdot)e^{\beta\cdot} \in L(-\infty, 0]; \\ &X_U(0) = X_{U_0} > 0, \qquad X_I(0) = X_{I_0} > 0, \qquad I_R(0) = I_{R_0} > 0, \qquad I_A(0) = I_{A_0} > 0. \end{aligned} \tag{2.2}$$

Similar to Lemma 1 in [9], we easily prove that the solution of system (2.1) remains positive whenever it exists.

3. The local stability of the equilibrium and Hopf bifurcation

It is clear that the equations related to $B(t)$ and $I_R(t)$ are independent to the other three equations of system (2.1). In this paper, we are mainly devoted to investigating the dynamical properties for $B(t)$ and $I_R(t)$. In other words, only the following subsystem will be focused on in subsequent discussion:

$$\begin{cases} \dfrac{dB(t)}{dt} = \alpha_{20}\left(1 + \displaystyle\int_{-\infty}^{t} \beta e^{-\beta(t-u)} \frac{B(u)}{B_0}\,du - \frac{B(t)}{\sigma}\right)B(t) - \alpha_3 B(t) I_R(t), \\ \dfrac{dI_R(t)}{dt} = S_{I_R} + \beta_1 B(t) - \mu_{I_R} I_R(t), \end{cases} \tag{3.1}$$

with initial values

$$B(s) = \psi(s), \quad s \in (-\infty, 0] \quad \text{with } \psi(0) > 0,\ \psi(s) \geqslant 0,\ s \in (-\infty, 0),\ \psi(\cdot)e^{\beta\cdot} \in L(-\infty, 0],$$
$$I_R(0) = I_{R_0} > 0. \tag{3.2}$$

Let

$$X(t) = \int_{-\infty}^{t} \beta e^{-\beta(t-u)} B(u)\,du. \tag{3.3}$$

Then by linear chain trick technology [24,25], the two-dimensional system (3.1) can be equivalently transformed into a three-dimensional system

$$\begin{cases} \dfrac{dB(t)}{dt} = \alpha_{20}\left(1 + \dfrac{X(t)}{B_0} - \dfrac{B(t)}{\sigma}\right)B(t) - \alpha_3 B(t) I_R(t), \\ \dfrac{dI_R(t)}{dt} = S_{I_R} + \beta_1 B(t) - \mu_{I_R} I_R(t), \\ \dfrac{dX(t)}{dt} = \beta B(t) - \beta X(t), \end{cases} \tag{3.4}$$

with initial values

$$B(0) = \psi(0), \qquad I_R(0) = I_{R_0} > 0 \quad \text{and} \quad X(0) = \int_{-\infty}^{0} \beta e^{\beta s} \psi(s)\,ds. \tag{3.5}$$

Remark 1. If $(B(t), I_R(t))$ is a solution of system (3.1)–(3.2), then $(B(t), I_R(t), X(t))$ obviously solves system (3.4)–(3.5), where $X(t)$ is defined by (3.3). Conversely, if $(B(t), I_R(t), X(t))$ is a solution of system (3.4)–(3.5), then $X(t)$ satisfies (3.3), and further then $(B(t), I_R(t))$ solves system (3.1)–(3.2) for $t \geqslant 0$.

For the convenience of description, we introduce the following denotation:

$$R_0 = \frac{\alpha_3 S_{I_R}}{\alpha_{20}\mu_{I_R}}, \qquad a = \frac{1}{B_0} \quad \text{and} \quad \epsilon = \frac{1}{\sigma} - a.$$

Clearly, $\epsilon > -a$ and $\epsilon < \frac{1}{\sigma}$. The biological meaning of R_0 will be given in Section 5.

For system (3.4)–(3.5), we easily obtain the following theorem with respect to the existence of its equilibrium points. Here, the proof is omitted.

Theorem 3.1. *There exists a unique positive equilibrium point $E^* = (B^*, I_R^*, X^*)$ if and only if $(1 - R_0)(\epsilon + \frac{\beta_1 R_0}{S_{I_R}}) > 0$, while there always exists a bacteria free equilibrium point $E_0 = (0, I_R^0, 0)$, where*

$$B^* = X^* = \frac{(1 - R_0)}{\epsilon + \frac{\beta_1 R_0}{S_{I_R}}}, \qquad I_R^* = \frac{S_{I_R}}{\mu_{I_R}} + \frac{\beta_1}{\mu_{I_R}} B^* \quad \text{and} \quad I_R^0 = \frac{S_{I_R}}{\mu_{I_R}}.$$

Next, we investigate the local stability of each equilibrium point of system (3.4).

Theorem 3.2.

(1) *If $R_0 < 1$, then E_0 is unstable, while if $R_0 > 1$, then E_0 is locally asymptotically stable.*
(2) *If $R_0 < 1$ and one of the following conditions hold, then E^* is locally asymptotically stable when it exists*:
- $\epsilon < 0$, β *is small enough,*
- $\epsilon \geqslant 0$.

(3) *If $R_0 > 1$, then E^* is unstable when it exists.*

Proof. (1) The Jacobian matrix of system (3.4) at bacteria free equilibrium point E_0, has the form

$$J := \begin{pmatrix} \alpha_{20}(1-R_0) & 0 & 0 \\ \beta_1 & -\mu_{I_R} & 0 \\ \beta & 0 & -\beta \end{pmatrix}.$$

It is clear that matrix J has eigenvalues $\alpha_{20}(1-R_0)$, $-\mu_{I_R}$ and $-\beta$. Therefore, if $R_0 < 1$, the bacteria free equilibrium point is unstable, while if $R_0 > 1$, it is locally asymptotically stable.

(2) The Jacobian matrix of system (3.4) at positive equilibrium point E^* has the form

$$M := \begin{pmatrix} -\alpha_{20}B^*(a+\epsilon) & -\alpha_3 B^* & \alpha_{20}B^* a \\ \beta_1 & -\mu_{I_R} & 0 \\ \beta & 0 & -\beta \end{pmatrix}.$$

The characteristic equation of M is

$$\lambda^3 + a_1\lambda^2 + a_2\lambda + a_3 = 0, \tag{3.6}$$

where λ is a complex number and

$$\begin{aligned} a_1 &= \alpha_{20}B^*(a+\epsilon) + \mu_{I_R} + \beta, \\ a_2 &= \alpha_{20}B^*\epsilon\mu_{I_R} + \beta_1\alpha_3 B^* + \alpha_{20}B^* a\mu_{I_R} + \mu_{I_R}\beta + \alpha_{20}B^*\epsilon\beta, \\ a_3 &= B^*\beta(\alpha_{20}\epsilon\mu_{I_R} + \beta_1\alpha_3) = \beta\mu_{I_R}\alpha_{20}(1-R_0). \end{aligned}$$

Clearly, $a_1 > 0$. After tedious computation, we get

$$\begin{aligned} a_1a_2 - a_3 = {} & 2\alpha_{20}^2 B^{*2} a\epsilon\mu_{I_R} + \alpha_{20}B^{*2}a\beta_1\alpha_3 + \alpha_{20}^2 B^{*2}a^2\mu_{I_R} + 2\alpha_{20}B^* a\mu_{I_R}\beta + \alpha_{20}^2 B^{*2}a\epsilon\beta + \alpha_{20}B^*\epsilon\mu_{I_R}^2 \\ & + \mu_{I_R}\beta_1\alpha_3 B^* + \alpha_{20}B^* a\mu_{I_R}^2 + \mu_{I_R}^2\beta + 2\alpha_{20}B^*\epsilon\mu_{I_R}\beta + \mu_{I_R}\beta^2 + \alpha_{20}B^*\epsilon\beta^2 + \alpha_{20}^2 B^{*2}\epsilon^2\mu_{I_R} \\ & + \alpha_{20}^2 B^{*2}\epsilon\beta_1\alpha_3 + \alpha_{20}^2 B^{*2}\epsilon^2\beta. \end{aligned} \tag{3.7}$$

Then, if $\epsilon \geqslant 0$, or $\epsilon < 0$, β is small enough and $R_0 < 1$, we have $a_2, a_3 > 0$ and $a_1a_2 - a_3 > 0$, which means E^* is locally asymptotically stable when it exists.

(3) If $R_0 > 1$, we have $a_3 < 0$. By Routh–Hurwitz criterion, E^* is unstable. □

Note that the lines $R_0 = 1$ and $\epsilon = -\frac{\beta_1 R_0}{S_{I_R}}$ split the semiplane $\{(R_0, \epsilon) \mid R_0 > 0\}$ into four open regions. As a result of above discussion, E_0 exists in all of the regions, while E^* only exists in two of them. Therefore, we easily get the bifurcation diagram shown in Fig. 1 of system (3.4) in (R_0, ϵ) plane. Furthermore, in each region, the locally phase portrait with respect to B and I_R is depicted in Fig. 2.

Clearly, when $R_0 = 1$, the matrix J has eigenvalues: $\lambda_1 = 0$, $\lambda_2 = -\mu_{I_R}$ and $\lambda_3 = -\beta$. That is to say E_0 is not hyperbolic. Therefore, we will investigate the dynamics of E_0 by using the center manifold theorem [26].

Firstly, we shift E_0 to origin by $y_1(t) = B(t)$, $y_2(t) = I_R(t) - I_R^0$ and $y_3(t) = X(t)$ so that system (3.4) becomes

$$\begin{cases} \dfrac{dy_1(t)}{dt} = \alpha_{20}a y_1(t)y_3(t) - \alpha_{20}(a+\epsilon)y_1(t)^2 - \alpha_3 y_1(t)y_2(t), \\ \dfrac{dy_2(t)}{dt} = \beta_1 y_1(t) - \mu_{I_R} y_2(t), \\ \dfrac{dy_3(t)}{dt} = \beta y_1(t) - \beta y_3(t). \end{cases} \tag{3.8}$$

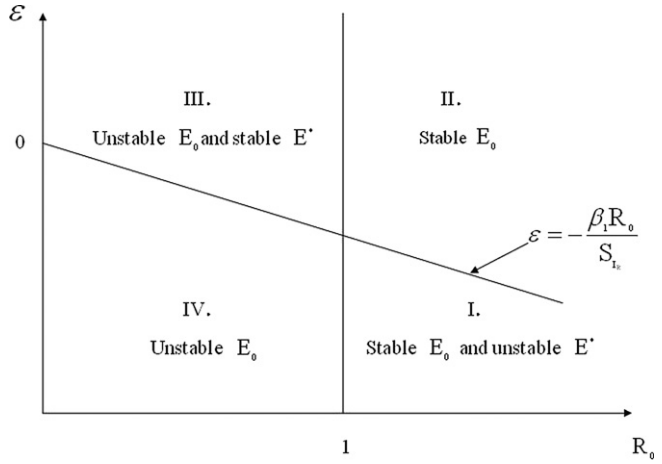

Fig. 1. Bifurcation diagram of system (3.4) in (R_0, ϵ) plane for $R_0 > 0$.

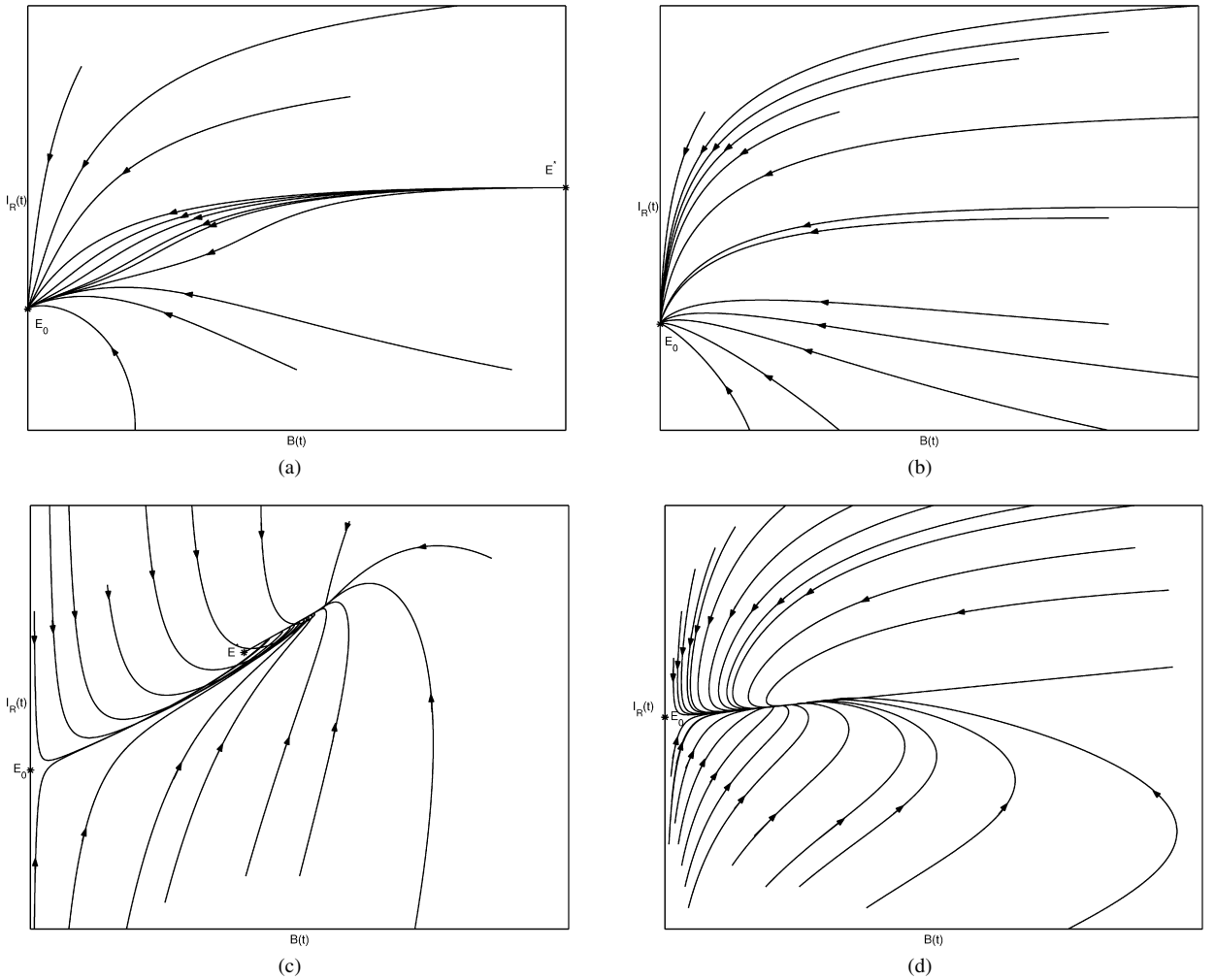

Fig. 2. (a) is the phase portraits for stable E_0 and unstable E^* in the region I, (b) is the phase portraits for stable E_0 in the region II, (c) is the phase portraits for the unstable E_0 and stable E^* with small ρ and $\epsilon < 0$ in the region III, (d) is the unstable E_0 in the region IV.

Secondly, we define

$$\begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} = T \begin{pmatrix} y_1(t) \\ y_2(t) \\ y_3(t) \end{pmatrix} \quad \text{with } T = \begin{pmatrix} 1 & 0 & 0 \\ -\frac{\beta_1}{\mu_{I_R}} & 1 & 0 \\ -1 & 0 & 1 \end{pmatrix},$$

which transforms system (3.4) into the following standard form:

$$\begin{pmatrix} \frac{dx_1(t)}{dt} \\ \frac{dx_2(t)}{dt} \\ \frac{dx_2(t)}{dt} \end{pmatrix} = \begin{pmatrix} 0 & 0 & 0 \\ 0 & -\mu_{I_R} & 0 \\ 0 & 0 & -\beta \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} + \begin{pmatrix} f_1(x_1(t), x_2(t), x_3(t)) \\ f_2(x_1(t), x_2(t), x_3(t)) \\ f_3(x_1(t), x_2(t), x_3(t)) \end{pmatrix}, \tag{3.9}$$

where

$$\begin{aligned} f_1 &= \alpha_{20} a x_1(t)\big(x_1(t) + x_3(t)\big) - \alpha_{20}(a+\epsilon)x_1^2(t) - \alpha_3 x_1(t)\left(\frac{\beta_1}{\mu_{I_R}} x_1(t) + x_2(t)\right), \\ f_2 &= -\frac{\beta_1}{\mu_{I_R}} f_1, \\ f_3 &= -f_1. \end{aligned}$$

By the existence theorem in the center manifold theory [26], there exists a center manifold for system (3.9), which can be locally expressed as follows

$$W^c(0) = \left\{(x_1, x_2, x_3) \in \mathbb{R}^3 \;\middle|\; x_2 = h_1(x_1),\ x_3 = h_2(x_1),\ \|x_1\| < \delta,\ h_i(0) = 0,\ Dh_i(0) = 0 \mid i = 1, 2 \text{ and } \delta > 0\right\}$$

with δ sufficiently small, and Dh_i the derivative of h_i with respect to x_1.

We now compute the center manifold $W^c(0)$. Assume that $h_i(x_1)$, $i = 1, 2$, have the following forms:

$$\begin{aligned} x_2 &= h_1(x_1) = h_{11}x_1^2 + h_{12}x_1^3 + \cdots, \\ x_3 &= h_2(x_1) = h_{21}x_1^2 + h_{22}x_1^3 + \cdots. \end{aligned} \tag{3.10}$$

By the invariance of $W^c(0)$ under the dynamics of (3.9), the center manifold must satisfy

$$Dh \cdot f_1(x_1, h_1, h_2) - Bh - f(x_1, h_1, h_2) = 0, \tag{3.11}$$

where

$$h = \begin{pmatrix} h_1 \\ h_2 \end{pmatrix}, \quad f = \begin{pmatrix} f_2 \\ f_3 \end{pmatrix}, \quad B = \begin{pmatrix} -\mu_{I_R} & 0 \\ 0 & -\beta \end{pmatrix}.$$

Substituting (3.10) into (3.11), and then equating coefficients on each power of x_1 to zero, yields

$$\begin{aligned} h_{11} &= \frac{\beta_1(\alpha_{20}\epsilon\mu_{I_R} + \beta\alpha_3)}{\mu_{I_R}^3}, \\ h_{12} &= \frac{\beta_1(-\alpha_{20}\epsilon\mu_{I_R} - \beta_1\alpha_3)(-2\alpha_{20}\epsilon\mu_{I_R}\beta - 3\beta_1\alpha_3\beta + \alpha_{20}a\mu_{I_R})}{\mu_{I_R}^5\beta}, \\ h_{21} &= \frac{\alpha_{20}\epsilon\mu_{I_R} + \alpha_3\beta_1}{\mu_{I_R}\beta}, \\ h_{22} &= \frac{(-\alpha_{20}\epsilon\mu_{I_R} - \alpha_3\beta_1)(-2\alpha_3\beta_1\mu_{I_R} - \beta_1\alpha_3\beta - 2\alpha_{20}\epsilon\mu_{I_R}^2 + \alpha_{20}a\mu_{I_R}^2)}{\beta^2\mu_{I_R}^3}. \end{aligned} \tag{3.12}$$

Substituting (3.12) into (3.10), yields

$$h_1(x_1) = \frac{\beta_1(\alpha_{20}\epsilon\mu_{I_R} + \beta\alpha_3)}{\mu_{I_R}^3}x_1^2 + \frac{\beta_1(-\alpha_{20}\epsilon\mu_{I_R} - \beta_1\alpha_3)(-2\alpha_{20}\epsilon\mu_{I_R}\beta - 3\beta_1\alpha_3\beta + \alpha_{20}a\mu_{I_R})}{\mu_{I_R}^5\beta}x_1^3 + \cdots,$$
$$h_2(x_1) = \frac{\alpha_{20}\epsilon\mu_{I_R} + \alpha_3\beta_1}{\mu_{I_R}\beta}x_1^2 \quad + \frac{(-\alpha_{20}\epsilon\mu_{I_R} - \alpha_3\beta_1)(-\alpha_3\beta_1(2\mu_{I_R} + \beta) - \alpha_{20}\mu_{I_R}^2(2\epsilon - a))}{\beta^2\mu_{I_R}^3}x_1^3 + \cdots. \tag{3.13}$$

Finally, substituting (3.13) into (3.9), we obtain the vector field reduced to the center manifold

$$\frac{dx_1(t)}{dt} = -\left(\alpha_{20}\epsilon + \frac{\alpha_3\beta_1}{\mu_{I_R}}\right)x_1^2(t) - \left(\frac{\alpha_3\beta_1\alpha_{20}(\epsilon\beta - a\mu_{I_R})}{\mu_{I_R}^2} + \frac{\alpha_3^2\beta_1^2}{\mu_{I_R}^3} - \frac{\alpha_{20}^2a\epsilon}{\beta}\right)x_1^3(t) + \cdots. \tag{3.14}$$

Then, we have the following results about the nonhyperbolic equilibrium point E_0.

Theorem 3.3. *Under the condition of $R_0 = 1$, the bacteria free equilibrium point E_0 is locally asymptotically stable if $\epsilon > -\frac{\beta_1 R_0}{S_{I_R}}$, and unstable if $\epsilon < -\frac{\beta_1 R_0}{S_{I_R}}$.*

Let

$$\max\left\{-\frac{(\beta_1\alpha_3 + \alpha_{20}a\mu_{I_R})B^* + \mu_{I_R}\beta}{\alpha_{20}B^*(\mu_{I_R} + \beta)}, -\frac{\beta_1\alpha_3}{\alpha_{20}\mu_{I_R}}\right\} < \epsilon < 0. \tag{3.15}$$

Clearly, (3.15) results in $a_2, a_3 > 0$.

Next, under the condition of (3.15), we analyze the qualitative properties of system (3.4). For the end, we first denote the right side of (3.7) as

$$A_1\beta^2 + A_2\beta + A_3 := \Psi(\beta), \tag{3.16}$$

where

$$A_1 = \alpha_{20}B^*\epsilon + \mu_{I_R},$$
$$A_2 = 2\alpha_{20}B^*a\mu_{I_R} + \alpha_{20}^2B^{*2}a\epsilon + \alpha_{20}^2B^{*2}\epsilon^2 + \mu_{I_R}^2 + 2\alpha_{20}B^*\epsilon\mu_{I_R},$$
$$A_3 = \alpha_{20}^2B^{*2}(a+\epsilon)^2\mu_{I_R} + \alpha_{20}B^{*2}(a+\epsilon)\beta_1\alpha_3 + \alpha_{20}B^*(a+\epsilon)\mu_{I_R}^2 + \mu_{I_R}\beta_1\alpha_3B^*.$$

Clearly, $A_3 > 0$, for all $\epsilon > -a$.

By Routh–Hurwitz criterion, under condition of (3.15), characteristic equation (3.6) has a pair of purely imaginary roots if and only if there exists a positive number β^* such that $\Psi(\beta^*) = 0$. Obviously, if such β^* exists, a Hopf bifurcation maybe occurs near the positive equilibrium point as β passes through β^*, otherwise, the positive equilibrium point is locally asymptotically stable.

To study the existence of β^*, we first introduce the Sturm sequence [23].

Suppose l is a polynomial function that has no repeated roots. Then l and its derivation l' are relatively prime. Let $l = l_0$ and $l' = l_1$. We obtain the following sequence of equations by the division algorithm:

$$l_0 = q_0l_1 - l_2,$$
$$l_1 = q_1l_2 - l_3,$$
$$\vdots$$
$$l_{s-2} = q_{s-2}l_{s-1} - K,$$

where K is a constant.

The sequence of Sturm functions $l_0, l_1, \ldots, l_{s-1}, l_s \equiv K$ is called a Sturm chain. We may determine the number of real roots of the polynomial l in any interval in the following manner: plug in each endpoint of the interval, and obtain a sequence of signs. The number of real roots in the interval is the difference between the number of sign changes in the sequence at each endpoint.

We now take the Sturm chain of the polynomial (3.16), and denote them as l_0, l_1, l_2. It is easy to get that

$$l_0 = A_1\beta^2 + A_2\beta + A_3,$$
$$l_1 = 2A_1\beta + A_2,$$
$$l_2 = -A_3 + \frac{A_2^2}{4A_1}.$$

We evaluate the nonnegative real line, i.e. from 0 to ∞, and construct a table of the signs at these endpoints.

	0	∞
l_0	+	$\operatorname{sgn}(A_1)$
l_1	$\operatorname{sgn}(A_2)$	$\operatorname{sgn}(A_1)$
l_2		

Denote u and v as the total number of sign changes of l_0, l_1, l_2 at 0 and ∞, respectively. Let $\lambda_{1,2}$ be a pair of conjugated complex roots of Eq. (3.6) when they exist. Then, under the condition of (3.15), we have the following theorem on the existence of the Hopf bifurcation at positive equilibrium point E^*. Here, the proof is also omitted.

Theorem 3.4.

(1) *If $l_2 > 0$, $A_1, A_2 > 0$, we have $u - v = 0$. That is, E^* is locally asymptotically stable*;
(2) *If $l_2 > 0$, $A_2 < 0$ and $A_3 > 0$ we have $u - v = 2$. That is, there exists two positive constants β_1^* and β_2^* such that $\Psi(\beta_i^*) = 0$. If the transversality condition $\frac{d\mathfrak{Re}\,\lambda_{1,2}}{d\beta}|_{\beta=\beta_i^*} \neq 0$ holds, then a Hopf bifurcation occurs at E^* when β passes through each critical value β_i^**;
(3) *If $l_2 < 0$, $A_1, A_2 > 0$, we have $u - v = 0$. That is, E^* is locally asymptotically stable*;
(4) *If $l_2 < 0$, $A_1 > 0$ and $A_2 < 0$, we have $u - v = 0$. That is, E^* is locally asymptotically stable*;
(5) *If $l_2 < 0$, $A_1 < 0$ and $A_2 > 0$, we have $u - v = 1$. That is, there exists a positive constant β^* such that $\Psi(\beta^*) = 0$. If the transversality condition $\frac{d\mathfrak{Re}\,\lambda_{1,2}}{d\beta}|_{\beta=\beta^*} \neq 0$ holds, then a Hopf bifurcation occurs at E^* when β passes through the critical value β^**;
(6) *If $l_2 < 0$, $A_1 < 0$ and $A_2 < 0$ we have $u - v = 1$. That is, there exists a positive constant β^* such that $\Psi(\beta^*) = 0$. If the transversality condition $\frac{d\mathfrak{Re}\,\lambda_{1,2}}{d\beta}|_{\beta=\beta^*} \neq 0$ holds, then a Hopf bifurcation occurs at E^* when β passes through the critical value β^*.*

Next, supposing there exists a positive number β^* satisfies $\Psi(\beta^*) = 0$ and $\frac{d\mathfrak{Re}\,\lambda_{1,2}}{d\beta}|_{\beta=\beta^*} \neq 0$, we check the stability of the bifurcating periodic orbits which occurs near the positive equilibrium point. For this end, we need to compute the index number in the Hopf bifurcation theorem [27] by means of the center manifold theorem [26].

We first transfer E^* to origin via $y_1(t) = B(t) - B^*$, $y_2(t) = I_R(t) - I_R^*$ and $y_3(t) = X(t) - X^*$. Then, system (3.4) becomes

$$\begin{cases} \dfrac{dy_1(t)}{dt} = -\alpha_{20}B^*(a+\epsilon)y_1(t) - \alpha_3 B^* y_2(t) + \alpha_{20}aB^* y_3(t) + \alpha_{20}a y_1(t)y_3(t) \\ \qquad\qquad - \alpha_3 y_1(t)y_2(t) - \alpha_{20}(a+\epsilon)x_1^2(t), \\ \dfrac{dy_2(t)}{dt} = \beta_1 y_1(t) - \mu_{I_R} y_2(t), \\ \dfrac{dy_3(t)}{dt} = \beta^* y_1(t) - \beta^* y_3(t). \end{cases} \tag{3.17}$$

Obviously, the characteristic equation of the Jacobian matrix of system (3.17) at origin has a simple pair of pure imaginary roots $\lambda_{1,2} = \pm\omega i$ and a negative real root $\lambda_3 = -a_1$, where $a_1 = \alpha_{20}B^*(a+\epsilon) + \mu_{I_R} + \beta^*$, $\omega > 0$ and $\omega^2 = a_2 = \alpha_{20}B^*\epsilon\mu_{I_R} + \beta_1\alpha_3 B^* + \alpha_{20}B^* a\mu_{I_R} + \mu_{I_R}\beta^* + \alpha_{20}B^*\epsilon\beta^*$.

Let

$$\begin{pmatrix} y_1(t) \\ y_2(t) \\ y_3(t) \end{pmatrix} = T \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} \quad \text{with } T = \begin{pmatrix} 0 & 1 & 1 \\ -n_1\omega & \mu_{I_R} n_1 & -n_2 \\ -n_3\omega & \beta n_3 & -n_4 \end{pmatrix},$$

where $n_1 = \frac{\beta_1}{\mu_{I_R}^2+\omega^2}$, $n_2 = \frac{\beta_1}{a_1-\mu_{I_R}}$, $n_3 = \frac{\beta^*}{\beta^{*2}+\omega^2}$ and $n_4 = \frac{\beta^*}{a_1-\beta^*}$.

Then, system (3.17) can be transformed into

$$\begin{pmatrix} \frac{dx_1(t)}{dt} \\ \frac{dx_2(t)}{dt} \\ \frac{dx_3(t)}{dt} \end{pmatrix} = \begin{pmatrix} 0 & -\omega & 0 \\ \omega & 0 & 0 \\ 0 & 0 & -a_1 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \\ x_3(t) \end{pmatrix} + \begin{pmatrix} f_1(x_1(t), x_2(t), x_3(t)) \\ f_2(x_1(t), x_2(t), x_3(t)) \\ f_3(x_1(t), x_2(t), x_3(t)) \end{pmatrix}, \tag{3.18}$$

where

$$\begin{aligned} f_1 &= \frac{-\mu_{I_R} n_1 n_4 + n_2 \beta^* n_3}{-\omega(n_1 n_4 + n_1 \beta^* n_3 - n_3 n_2 - n_3 \mu_{I_R} n_1)} \big[\alpha_{20} a\big(-\omega n_3 x_1 + \beta^* n_3 x_2 - n_4 x_3\big) \\ &\quad - \alpha_3(-\omega n_1 x_1 + \mu_{I_R} n_1 x_2 - n_2 x_3) - \alpha_{20}(a+\epsilon)(x_2+x_3)\big](x_2+x_3), \\ f_2 &= \frac{-\omega n_1 n_4 + \omega n_3 n_2}{-\omega(n_1 n_4 + n_1 \beta^* n_3 - n_3 n_2 - n_3 \mu_{I_R} n_1)} \big[\alpha_{20} a\big(-\omega n_3 x_1 + \beta^* n_3 x_2 - n_4 x_3\big) \\ &\quad - \alpha_3(-\omega n_1 x_1 + \mu_{I_R} n_1 x_2 - n_2 x_3) - \alpha_{20}(a+\epsilon)(x_2+x_3)\big](x_2+x_3), \\ f_3 &= \frac{-\omega n_1 \beta^* n_3 + \omega n_3 \mu_{I_R} n_1}{-\omega(n_1 n_4 + n_1 \beta^* n_3 - n_3 n_2 - n_3 \mu_{I_R} n_1)} \big[\alpha_{20} a\big(-\omega n_3 x_1 + \beta^* n_3 x_2 - n_4 x_3\big) \\ &\quad - \alpha_3(-\omega n_1 x_1 + \mu_{I_R} n_1 x_2 - n_2 x_3) - \alpha_{20}(a+\epsilon)(x_2+x_3)\big](x_2+x_3). \end{aligned}$$

By the existence theorem in the center manifold theory [26], there exists a center manifold for system (3.18), locally we have

$$W^c(0) = \big\{(x_1, x_2, x_3) \in \mathbb{R}^3 \,\big|\, x_3 = h(x_1, x_2),\ |x_1| + |x_2| < \delta,\ h(0,0) = 0,\ Dh(0,0) = 0\big\}$$

for sufficiently small δ.

We now compute $W^c(0)$. Assume that $h(x_1, x_2)$ has the following forms:

$$x_3 = h(x_1, x_2) = h_1 x_1^2 + h_2 x_1 x_2 + h_3 x_2^2 + \cdots. \tag{3.19}$$

Using the invariance of $W^c(0)$ under the dynamics generated by (3.18), we obtain that the center manifold must satisfy

$$Dh \cdot \big(Ax + f'(x)\big) - Bh - g(x) = 0, \tag{3.20}$$

where

$$A = \begin{pmatrix} 0 & -\omega \\ \omega & 0 \end{pmatrix}, \quad B = -a_1, \quad x = \begin{pmatrix} x_1 \\ x_2 \\ h(x_1, x_2) \end{pmatrix}, \quad f'(x) = \begin{pmatrix} f_1(x) \\ f_2(x) \end{pmatrix}, \quad g(x) = f_3(x).$$

Substituting (3.19) into (3.20), and then equating terms of like powers to zero yields

$$\begin{aligned} h_1 &= \frac{n_3 n_1 \omega^2(-\beta^* + \mu_{I_R})(-2\mu_{I_R} n_1 \alpha_3 + n_3 \alpha_{20} a a_1 + 2 n_3 \beta^* \alpha_{20} a - 2\alpha_{20}(a+\epsilon) - n_1 \alpha_3 a_1)}{(4\omega^2 + a_1^2)(-n_1 n_4 - n_1 \beta^* n_3 + n_3 n_2 + n_3 \mu_{I_R} n_1) a_1}, \\ h_2 &= -\frac{\omega n_3 n_1(-\beta^* + \mu_{I_R})(-2\mu_{I_R} n_1 \alpha_3 + n_3 \alpha_{20} a(a_1 + 2\beta^*) - 2\alpha_{20}(a+\epsilon) - n_1 \alpha_3 a_1)}{(4\omega^2 + a_1^2)(-n_1 n_4 - n_1 \beta^* n_3 + n_3 n_2 + n_3 \mu_{I_R} n_1)}, \\ h_3 &= \frac{n_3 n_1(-\beta^* + \mu_{I_R})}{(4\omega^2 + a_1^2)(-n_1 n_4 - n_1 \beta^* n_3 + n_3 n_2 + n_3 \mu_{I_R} n_1) a_1} \big[-\mu_{I_R} n_1 a_1^2 \alpha_3 - 2\mu_{I_R} n_1 \omega^2 \alpha_3 \\ &\quad + n_1 \omega^2 \alpha_3 a_1 - \big(2\omega^2 + a_1^2\big)\alpha_{20}(a+\epsilon) + n_3 \alpha_{20} a\big(a_1^2 \beta^* - \omega^2 a_1 + 2\omega^2 \beta^*\big)\big]. \end{aligned} \tag{3.21}$$

Substituting (3.19) into (3.18) and using (3.21), we obtain the vector field reduced to the center manifold

$$\begin{pmatrix} \frac{dx_1(t)}{dt} \\ \frac{dx_2(t)}{dt} \end{pmatrix} = \begin{pmatrix} 0 & -\omega \\ \omega & 0 \end{pmatrix} \begin{pmatrix} x_1(t) \\ x_2(t) \end{pmatrix} + \begin{pmatrix} f_1(x_1(t), x_2(t), h(x_1(t), x_2(t))) \\ f_2(x_1(t), x_2(t), h(x_1(t), x_2(t))) \end{pmatrix}. \tag{3.22}$$

For the convenience of denotation, we respectively denote f^1 and f^2 as f_1 and f_2. Therefore, we can compute the index A in [27] as follows

$$\begin{aligned}
A &= \frac{1}{16}\big[f^1_{x_1x_1x_1} + f^1_{x_1x_2x_2} + f^2_{x_1x_1x_2} + f^2_{x_2x_2x_2}\big] \\
&\quad + \frac{1}{16\omega}\big[f^1_{x_1x_2}\big(f^1_{x_1x_1} + f^1_{x_2x_2}\big) - f^2_{x_1x_2}\big(f^2_{x_1x_1} + f^2_{x_2x_2}\big) - f^1_{x_1x_1}f^2_{x_1x_1} + f^1_{x_2x_2}f^2_{x_2x_2}\big] \\
&= \frac{-\mu_{I_R}n_1n_4 + \beta^*n_2n_3}{8}\big[k_1\big(\alpha_{20}\big(a\beta^*n_3 - an_4\big) - 2(a+\epsilon) - \alpha_3(\mu_{I_R}n_1 - n_2)\big) + k_2\omega(\alpha_3n_1 - \alpha_{20}an_3)\big] \\
&\quad + \frac{3k_1\omega(-\mu_{I_R}n_1n_4 + \beta^*n_2n_3)}{8}(-\alpha_{20}an_3 + \alpha_3\omega n_1) \\
&\quad + \frac{k_1\omega^2(-n_1n_4 + n_2n_3)}{8a_1}\big[a_1(-\alpha_{20}an_3 + \alpha_3n_1) + \alpha_{20}\big(a\big(-\beta^*n_3 + n_4\big) - 2(a+\epsilon)\big) + \alpha_3(\mu_{I_R}n_1 - n_2)\big] \\
&\quad + \frac{k_2\omega(n_2n_3 - n_1n_4)}{8}\big[\alpha_{20}\big(a\big(\beta^*n_3 + n_4\big) - (a+\epsilon)\big) + \alpha_3(n_2 - \mu_{I_R}n_1)\big] \\
&\quad + \frac{1}{16\omega}\big[(-n_3\omega\alpha_{20}a + \alpha_3\omega n_1)\big(-\mu_{I_R}n_1n_4 + n_2\beta^*n_3\big)^2\big(2n_3\alpha_{20}a\beta^* - 2\mu_{I_R}n_1\alpha_3 - 2\alpha_{20}(a+\epsilon)\big) \\
&\quad - (-\omega n_1n_4 + \omega n_3n_2)^2(-n_3\omega\alpha_{20}a + \alpha_3\omega n_1)\big(2n_3\alpha_{20}a\beta^* - 2\mu_{I_R}n_1\alpha_3 - 2\alpha_{20}(a+\epsilon)\big) \\
&\quad + \big(2n_3\alpha_{20}a\beta^* - 2\mu_{I_R}n_1\alpha_3 - 2\alpha_{20}(a+\epsilon)\big)^2\big(-\mu_{I_R}n_1n_4 + n_2\beta^*n_3\big)(-\omega n_1n_4 + \omega n_3n_2)\big],
\end{aligned}$$

where

$$\begin{aligned}
k_1 &= -\frac{(-\beta^* + \mu_{I_R})(-(2\mu_{I_R} + a_1)n_1\alpha_3 + \alpha_{20}(n_3aa_1 + 2n_3\beta^*a - 2(a+\epsilon)))\omega n_3n_1}{(4\omega^2 + a_1^2)(-n_1n_4 - n_1\beta^*n_3 + n_3n_2 + n_3\mu_{I_R}n_1)}, \\
k_2 &= \frac{(-\beta^* + \mu_{I_R})n_3n_1}{(4\omega^2 + a_1^2)(-n_1n_4 - n_1\beta^*n_3 + n_3n_2 + n_3\mu_{I_R}n_1)a_1}\big[-\mu_{I_R}n_1\alpha_3\big(a_1^2 + 2\omega^2\big) \\
&\quad + n_1\omega^2\alpha_3a_1 + \alpha_{20}\big(-\big(2\omega^2 + a_1^2\big)(a+\epsilon) + a\big(n_3\beta^*\big(a_1^2 + 2\omega^2\big) - \omega^2n_3a_1\big)\big)\big].
\end{aligned}$$

Under the conditions of $\frac{d\Re\mathrm{e}\,\lambda_{1,2}}{d\beta}|_{\beta=\beta^*} \neq 0$ and (3.15), using the Hopf bifurcation theorem [27], we obtain the following results about the stability of the periodic solutions bifurcated at E^*.

Theorem 3.5. *If $A < 0$, the periodic solution is stable, while if $A > 0$, the periodic solution is unstable. The case $A < 0$ is referred to as a supercritical bifurcation, and the case $A > 0$ is referred to as a subcritical bifurcation.*

4. The global stability of the positive equilibrium point

Clearly, (B^*, I_R^*) is a unique positive equilibrium point of system (3.1), and it exists if and only if the positive equilibrium point of system (3.4) (B^*, I_R^*, X^*) exists.

In this section, by constructing a reasonable Lyapunov function, we get a condition under which the positive equilibrium point of system (3.1) is globally stable. To the task, we define two new variables as $x(t) = \ln\frac{B(t)}{B^*}$ and $y(t) = I_R(t) - I_R^*$. Then system (3.1) can be transformed into

$$\begin{cases}
\dfrac{dx(t)}{dt} = \alpha_{20}\left(\displaystyle\int_{-\infty}^{t} \beta e^{-\beta(t-u)}\frac{B^*}{B_0}\big(e^{x(u)} - 1\big)\,du - \frac{e^{x(t)} - 1}{\sigma}B^*\right) - \alpha_3y(t), \\
\dfrac{dy(t)}{dt} = \beta_1\big(e^{x(t)} - 1\big)B^* - \mu_{I_R}y(t).
\end{cases} \tag{4.1}$$

It is easy to see that $(0, 0)$ is an equilibrium point of system (4.1) and its stability is equivalent to that of the positive equilibrium point of system (3.1).

Theorem 4.1. *If* $\epsilon > \frac{\beta_1 R_0}{S_{I_R}}$ *and* $R_0 < 1$, *then the positive equilibrium point* E^* *of system* (3.1) *exists and is globally asymptotically stable.*

Proof. Let $V_1(t) = |x(t)|$ and $V_2(t) = |y(t)|$. Calculating the respective upper-right derivative of $V_1(t)$ and $V_2(t)$ along the trajectory of system (4.1), yields

$$D^+V_1(t) = \operatorname{sgn} x(t)\left[\alpha_{20}\left(\int_{-\infty}^{t} \beta e^{-\beta(t-u)}\frac{B^*}{B_0}\big(e^{x(u)}-1\big)\,du - \frac{e^{x(t)}-1}{\sigma}B^*\right) - \alpha_3 y(t)\right] \tag{4.2}$$

and

$$D^+V_2(t) = \operatorname{sgn} y(t)\big(e^{x(t)}-1\big)B^*\beta_1 - \mu_{I_R}\big|y(t)\big|. \tag{4.3}$$

Let

$$V_3(t) = V_1(t) + \frac{\alpha_3}{\mu_{I_R}}V_2(t). \tag{4.4}$$

Substituting (4.2)–(4.3) into the upper-right of $V_3(t)$ yields

$$\begin{aligned} D^+V_3(t) &\leqslant \alpha_{20}\left(\int_{-\infty}^{t} \beta e^{-\beta(t-u)}\frac{B^*}{B_0}\big|e^{x(u)}-1\big|\,du - \frac{|e^{x(t)}-1|}{\sigma}B^*\right) - \operatorname{sgn} x(t)\alpha_3 y(t) \\ &\quad + \frac{\alpha_3}{\mu_{I_R}}\big(\big|e^{x(t)}-1\big|B^*\beta_1 - \mu_{I_R}\big|y(t)\big|\big) \\ &\leqslant \alpha_{20}\left(\int_{-\infty}^{t} \beta e^{-\beta(t-u)}\frac{B^*}{B_0}\big|e^{x(u)}-1\big|\,du - \frac{|e^{x(t)}-1|}{\sigma}B^*\right) + \frac{\alpha_3}{\mu_{I_R}}\big|e^{x(t)}-1\big|B^*\beta_1. \end{aligned} \tag{4.5}$$

Define

$$V_4(t) = \int_{-\infty}^{t} e^{-\beta(t-u)}\big|e^{x(u)}-1\big|\,du.$$

Clearly, the upper-right derivative of $V_4(t)$ along the trajectory of system (4.1) is

$$D^+V_4(t) = \big|e^{x(t)}-1\big| - \int_{-\infty}^{t} \beta e^{-\beta(t-u)}\big|e^{x(u)}-1\big|\,du. \tag{4.6}$$

Further define

$$V(t) = V_3(t) + \frac{\alpha_{20}B^*}{B_0}V_4(t). \tag{4.7}$$

By means of (4.5)–(4.6), it is easy to obtain that the upper-right derivative of $V(t)$ along the trajectory of system (4.1) satisfies

$$\begin{aligned} D^+V(t) &\leqslant \alpha_{20}\left(\int_{-\infty}^{t} \beta e^{-\beta(t-u)}\frac{B^*}{B_0}\big|e^{x(u)}-1\big|\,du - \frac{|e^{x(t)}-1|}{\sigma}B^*\right) + \frac{\alpha_3\beta_1 B^*}{\mu_{I_R}}\big|e^{x(t)}-1\big| \\ &\quad + \frac{\alpha_{20}B^*}{B_0}\left(\big|e^{x(t)}-1\big| - \int_{-\infty}^{t} \beta e^{-\beta(t-u)}\big|e^{x(u)}-1\big|\,du\right) \end{aligned}$$

$$= B^*\left[\alpha_{20}\left(\frac{1}{B_0} - \frac{1}{\sigma}\right) + \frac{\beta_1\alpha_3}{\mu_{I_R}}\right]\left|e^{x(t)} - 1\right|$$
$$= -B^*\alpha_{20}\left(\epsilon - \frac{\alpha_3\beta_1}{\alpha_{20}\mu_{I_R}}\right)\left|e^{x(t)} - 1\right|.$$

Then the positive equilibrium point of system (3.1) is globally asymptotically stable if $\epsilon > \frac{\alpha_3\beta_1}{\alpha_{20}\mu_{I_R}}$. □

5. Conclusions

In this paper, a model with delay quorum sensing describing the competition between bacteria and immune system is formulated. The bacteria free equilibrium point E_0 is locally asymptotically stable if $R_0 > 1$ (i.e. the bacteria will be cleared in the end), and unstable if $R_0 < 1$. Furthermore, by the center manifold theorem, the locally asymptotical stability of E_0 is discussed in Theorem 3.3 with $R_0 = 1$. For the positive equilibrium point E^*, if it exists, further either $R_0 < 1$, $B_0 < \sigma$ and β is small enough, or $B_0 \geqslant \sigma$ holds, it is locally asymptotically stable, otherwise, if $R_0 > 1$, it is unstable. Under the condition of $B_0 < \sigma$ and (3.15), using β as a bifurcation parameter, we discuss the existence and the stability of the Hopf bifurcation near of the positive equilibrium point E^*. In the sequel, by constructing a reasonable Lyapunov function, we get a condition under which the positive equilibrium point of system (3.1) is globally asymptotically stable.

From the biological viewpoint, it is noted that $\frac{S_{I_R}}{\mu_{I_R}}$ means the concentration of the initial immune cells at the uninfected equilibrium point. So the product of $\frac{S_{I_R}}{\mu_{I_R}}$ and the bacteria clearance factor α_3 measures the strength of the innate immune system defense against the bacteria challenge; while the bacteria productivity factor α_{20} measures the bacteria's offensive strength. So, with $R_0 = \frac{\alpha_3 S_{I_R}}{\alpha_{20}\mu_{I_R}}$, we can compare the strength of the immune system against the bacterial offensive. Thus, Theorem 3.2 has the biological explication: in the basin of attraction of E_0, bacteria will be cleared if $R_0 > 1$, namely, the strength of the innate immune system defense against the bacteria challenge is not weaker the bacteria's offensive strength; in the basin of attraction of E^*, bacteria co-exist with initial immune cells if $R_0 < 1$, namely, the bacterial challenge is weaker than bacteria's offensive strength.

Unfortunately, the global stability of bacteria free equilibrium point is not obtained. It will be solved in future.

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